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(54) Title: AMORPHOUS CARRIER MATERIALS FOR DRUG DELIVERY

(57) Abstract: Amorphous hydrophobically-derivatised carbohydrates (HDC) are used as effective carrier materials to deliver microparticles of a therapeutic agent to the lung.

# AMORPHOUS CARRIER MATERIALS FOR DRUG DELIVERY

## Field of the Invention

This invention relates to carrier particles for use in dry powder inhalers, and compositions containing the carrier particles.

## Background to the Invention

The administration of pharmaceutical agents via the pulmonary route is now of widespread interest and use.

Delivery of therapeutics is carried out using an inhaler device. Many different inhaler devices are known and there is much interest in developing improved devices which offer better delivery of the therapeutic and which are able to better regulate the dose administered.

One preferred type of device is the dry powder inhaler, which delivers dry powder particles comprising the therapeutic agent, using inhalation by the patient to expel the powders. However, improvement in this technology is desirable so that greater amounts of therapeutic can be delivered successfully to the patient.

One way of achieving this is to improve the formulations for use in the inhaler device to provide better flow properties on inhalation.

Typically, compositions used in the dry powder inhalers are formulated with suitable excipients which not only protect the therapeutic during storage, but which also aid the delivery process. One example is formulations of the therapeutic comprised within a solid carbohydrate matrix. These formulations are able to produce particles with good flow properties. An alternative example relies on small particles of the therapeutic agent which are then bound to a much larger carrier particle, which dissociates after inhalation, to release the therapeutic agent.

The therapeutic particles are usually small, spherical microspheres with a diameter in the range of 1 to 10 μm. The carrier particles are usually greater than 90 μm in diameter to achieve the flow characteristics required.

WO-A-95/11666 discloses dry powder formulations having carrier particles with good flow properties. The carrier particles are treated to dislodge small grains from this surface of the carrier to produce a high surface area on which the therapeutic particles can associate. It is stated that the carrier particles treated in this way reduce the amount of high energy sites which bind strongly to the therapeutic particles, preventing their release at the appropriate time. The carrier particles are crystalline sugar particles, preferably lactose particles.

Although many different formulations exist, there is still a need for improved formulations for inclusion in dry powder inhalers.

Summary of the Invention

The present invention is based on the surprising finding that hydrophobically-derivatised carbohydrates, when manufactured as amorphous particles, have beneficial properties making them very suitable as a carrier material.

According to one aspect of the invention, a particulate composition for pulmonary delivery comprises discrete particles of a therapeutic agent and of an amorphous carrier material, the carrier material being a hydrophobically derivatised carbohydrate (HDC).

According to a second aspect, amorphous particles consisting of a hydrophobically derivatised carbohydrate are used in the manufacture of a composition for the delivery of a therapeutic agent via the pulmonary route.

According to a third aspect, an inhaler device comprises a composition comprising a therapeutic agent bound to amorphous HDC carrier particles.

In one embodiment, the carrier material particles are 30-300 μm in diameter. In a preferred embodiment, their size is 50-150 μm.

The therapeutic agent may be any suitable agent, for example any beneficial peptide or protein which can exert a therapeutic effect when administered via the pulmonary route. In one embodiment, the therapeutic is insulin, in either its monomeric or hexameric form.

The amorphous nature of the carrier material may be achieved using any suitable technique. Preferably, the amorphous nature is achieved by spray-drying a suitable HDC.

Description of the Invention

The present invention requires the production of amorphous particles of HDCs. The invention therefore differs from much of the prior art which requires either crystalline materials, or non-derivatised sugars such as lactose.

The amorphous nature of the carrier particles is important as it imparts a relatively constant surface energy to the particles. This in turn allows the therapeutic agent to associate with the carrier in a uniform manner, and disassociation at the appropriate time is also achieved in a uniform way.

The term "amorphous" is applicable to any solid having a non-periodic atomic array. The term "glass" has conventionally been reserved for an amorphous solid which exhibits a glass transition (Tg).

For an amorphous solid, the essential aspect with which its structure differs from that of a crystalline solid is the absence of long range order. The matrix of equilibrium atomic positions is strongly disordered, and there is no longer any translational periodicity.

The formation of an amorphous solid is characterised by a change of phase (the glass transition temperature) represented by a shallow bend in a plot of volume versus temperature. An explanation of the formation of amorphous solids and of the glass transition temperature may be found in Craig *et al*, Int. J. Pharm., 1999; 179:179-207.

The carrier material may be any hydrophobically derivatised carbohydrate (HDC).

The term "hydrophobically derivatised carbohydrate" is intended to refer to any carbohydrate which has one or more (or all) of the sugar hydroxyl groups replaced with a hydrophobic substituent including, but not limited to, esters and ethers. The HDC will preferably be hydrophobic. The carbohydrate derivatives must be capable of forming a solid amorphous structure, preferably with a glass transition temperature greater than 20°C, preferably greater than 40°C and most preferably greater than 60°C. Suitable HDCs are described in WO-A-96/03978, the content of which is incorporated herein by reference. Preferred HDCs useful in the present invention include trehalose derivatives, including trehalose octaacetate (TOAC) and trehalose hexaacetate diisobutyrate (TIBAC).

Methods for producing the amorphous state for HDCs will be apparent to the skilled person. Suitable methods include spray-drying. Alternatively, a solution of the HDC can be dried at elevated temperatures, preferably under vacuum, to remove residual solvent content to achieve the amorphous, glassy state. The HDC could also be subjected to melt extrusion. The amorphous/glassy HDCs may then be ground or milled to produce the required size for use in the invention.

Typically, the residual solvent content for the HDC particles will be below 5%, preferably below 2% as measured by differential scanning calorimetry (DSC) Craig *et al*, *supra*. Spray-drying is a preferred way of achieving the amorphous state as it has the added benefit of producing particles with a suitable diameter as part of the overall process. Appropriate conditions for spray drying will be apparent to the skilled person.

The HDC carrier particles should be relatively large compared to the therapeutic particle. Typically, the carrier material will be approximately greater than 30 μm, preferably greater than 50 μm and most preferably between 50-300 μm in diameter.

When produced by spray-drying, the carrier material will usually be in a free-flowing state, readily useable in a dry powder inhaler.

Prior to inclusion in a dry powder inhaler, the carrier material should be blended with the therapeutic to be delivered. Methods for blending the components will be apparent to the skilled person.

The therapeutic may be in any suitable form useable in dry powder inhalers. Typically, the therapeutic will be a microparticle of approximately 1-20 μm, preferably 1-5 μm in diameter. Therapeutics suitable for use in the present invention include proteins, peptides, nucleic acids and chemical drugs.

Proteins which may be used according to the invention include insulin (for the treatment of diabetes), interferons, CM-CSF, cytokines, growth factors, antibodies, blood factors and therapeutic peptides. Other candidate therapeutics that may be used in the invention include anti-asthmatics (bronchodilators), e.g. salbutamol, anti-inflammatories and analgesics.

It is preferable if the therapeutic particles consist only of the active agent, as this provides advantages for controlling the dose administered to a patient. However, the active agent may be formulated with suitable excipients, which may be required for stabilising the active agent, for example on storage. The therapeutic particles may therefore include the active agent together with a carbohydrate or suitable salt.

Formulating the carrier material and therapeutic will be apparent to the skilled person based on typical formulation research. The dose administered to the patient will depend on the active agent to be given and the severity of the disease. Appropriate dose regimens can be readily determined by the skilled person.

The following Examples illustrate the invention.

Example 1

Amorphous TOAC was prepared by a quench of the molten material, allowing it to cool, then grinding in a pestle and mortar. This material was then sieved to obtain the required size fraction 63-100 μm. A sufficient mass of pre-screened inhalation-grade salbutamol sulphate was added to the amorphous TOAC above to provide 200 μg of salbutamol base per 20 mg of blend.

This mixture was then blended using a turbula until homogeneous, as determined by HPLC analysis of 5 aliquots from the powder bed. 20 mg of this blend was then placed into size 4 hard gelatin capsules and emitted into an MSLI at 50 l $min^{-1}$ from a Hovione Flow caps device. The mean % fine particle fraction (FPF) (<3.40

μm) was determined by HPLC analysis of the salbutamol content of the rinsings from a total of 5 runs.

Example 2

Example 1 was repeated using a 150-250 μm size fraction of the amorphous TOAC.

Example 3

A 150-200 μm size fraction of the mixture TOAC raw material was tested as in Example 1.

Example 4

A 150-250 μm size fraction of the crystalline trehalose was tested as in Example 1.

Example 5

Lactose 325M (74+15 μm) was tested as in Example 1 without screening.

The results are shown in Table 1.

Table 1

| No. | Material | % FPF | SD | %CV |
|---|---|---|---|---|
| 1 | 65-150 μm amorph. TOAC | 26.56 | 1.79 | 6.75 |
| 2 | 150-250 μm amorph. TOAC | 20.04 | 1.36 | 6.79 |
| 3 | 150-250 μm cryst. TOAC | 6.60 | 0.93 | 14.13 |
| 4 | 150-250 μm cryst. trehalose $T.2H_2O$ | 19.19 | 2.06 | 10.72 |
| 5 | 75 ± 15 μm lactose 325 M | 23.57 | 3.00 | 12.74 |

Table 1 shows that the amorphous HDC carriers demonstrate an improved emitted dose uniformity compared to both crystalline trehalose and lactose. A further surprising finding was that the amorphous carriers demonstrated a higher fine particle fraction than the same sized particles of the industry standard (Lactose 325 M).

CLAIMS

1. A particulate composition for pulmonary delivery, comprising discrete particles of a therapeutic agent and of an amorphous carrier material, wherein the carrier is a hydrophobically derivatised carbohydrate (HDC).

2. A composition according to claim 1, wherein the HDC is trehalose octaacetate.

3. A composition according to claim 1 or claim 2, wherein the carrier particles are 50 to 300 μm in diameter.

4. A composition according to any preceding claim, wherein the therapeutic agent is a protein or peptide.

5. A composition according to claim 4, wherein the therapeutic agent is insulin.

6. A composition according to any preceding claim, wherein the carrier particles are obtainable by spray-drying a HDC solution.

7. A composition according to any preceding claim, for therapeutic use.

8. Use of amorphous particles consisting of a hydrophobically derivatised carbohydrate, and particles of a therapeutic agent, in the manufacture of a medicament for the treatment of a disorder against which the therapeutic agent is active.

9. Use according to claim 8, wherein the agent is insulin and the disorder is diabetes.

10. Use according to claim 8, wherein the agent is a bronchodilator and the disorder is asthma.

11. An inhaler device comprising a composition according to any of claims 1 to 6.